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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,333	11/03/2003	Mark Ledeboer	VPI/02-116 US	5159

27916 7590 06/29/2006

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,333	LEDEBOER ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-29,31,32,34,35,37,38 and 40-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-29,31,32,34,35,37,38 and 40-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/6/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II drawn to compound of formula I wherein Z^1 id N and Z^7 is $C(U)_nR^y$, namely pyrimidine compounds in the reply filed on 4/6/2006 is acknowledged. In addition. amendment to claims 1, 28, 29, 31, 34-35, 37, 38 40-53 and 54 along with cancellation of non-elected claims 2-3, 30, 33, 36 and 39, is also acknowledged. Claims 1, 4-29, 31, 32, 34, 35, 37, 38 and 40-59 are now pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement field on 4/6/2004 are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-6 and 40-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 4-6 and 40-54, which are dependent on claim 1, recite the limitation of R^1 as optionally substituted phenyl, cycohexyl, cyclopentyl, pyridyl, morpholino, piperazinyl or piperidinyl groups but no antecedent basis for this limitation in the claim 1. In claim 1 Q is not a bond and hence the said dependent claims cannot have the above groups as substituents on the amino at 2- position of pyrimidine ring.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid arthritis, does not reasonably provide enablement for all diseases and disorders generically embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following apply.

The instant claims are drawn to a method of " inhibiting JAK kinase activity and treating or lessening the severity of a disease or disorder selected fro immune response, autoimmune diseases, neurodegenerative diseases solid or hematological malignancy" based on the mode of action of the instant compounds inhibitors of as JAK kinase activity which as recited reads on any or all diseases or disorders stated above for which there is no enabling disclosure.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of JAK kinase by the instant compounds, instant claims reaches through inhibiting and treating any or all above said diseases in general and thereby they lack adequate written description and enabling

disclosure in the specification. More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of JAK kinase, based on limited assay, it is claimed that treating any or all immune response, autoimmune diseases, neurodegenerative diseases and any or all cancers in general, which there is no enabling disclosure.

The scope of the claims includes treatment of any or all of diseases or conditions, which are not adequately enabled solely based on the activity of the compounds, provided in the specification at pages 1-6, and 83-84. The instant compounds are disclosed have JAK kinase inhibitory activity and it is recited that the instant compounds are useful in treating any or all diseases for which applicants provide no competent evidence. Reading specification it appears that instant compound is useful for treating all sorts of diseases including immune diseases, autoimmune diseases neurodegenerative diseases, solid and hematological malignancy etc. for which applicants have not provided any experimental support or nexus. Prior art searches do not lend support to, except for treating leukemia treatments of all diseases embraced in the claim language. That a single class of compounds can treat all or any disease /condition is an incredible finding for which applicants have not provided enabling disclosure and prior art search at the time of instant invention suggest the use of these inhibitors is still under experimental stage and speculative in nature. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such

as Alzheimer's disease, multiple sclerosis, ALS, cancer etc. are very difficult to treat and at present there is no known drug, which can successfully lessen the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition".

The scope of the claims, in addition to treating immune diseases, autoimmune diseases neurodegenerative diseases, includes any or all cancer (solid and hematological malignancy) due to JAK kinase inhibition for which there is no enabling disclosure. As recited, the scope of includes treatment of various cancers as the term cancer includes lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which are not adequately enabled solely based on the activity of the compounds provided in the specification. It appears that the applicants are asserting

that the embraced compounds because of their mode action as JAK kinase inhibitor that would be useful for all sorts of cancers and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions of compounds of claim 1 based on the generic definition of various variable groups as well as the thousand of diseases.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The state of the art is indicative of the requirement for undue experimentation. See Duhe et al. Cell Biochem. Biophys. 34(1): 17-59, 2001, Rane et al., Oncogene 19(49): 5662-79, 2000 (PubMed Abstracts provided). Also see Ivashkiv et al., Arthritis & Rheumatism 48(8)2092-2096, 2003.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating several diseases of that require JAK kinase inhibitory activity.

2) The state of the prior art: Recent publications at the time of instant invention suggest that use of JAK kinase inhibitor for treating disease are still in experimental stage. See Duhe et al., Rane et al., and Ivashkiv et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the therapeutic effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity

such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show therapeutic effect and the state of the art is that the effects of JAK kinase inhibitors are still in experimental stage

6) The breadth of the claims: The instant claims embrace treatment of all sorts of diseases including autoimmune diseases neurodegenerative diseases, solid and hematological malignancy etc.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7, 10-16, 19, 20, 22, 24, 25, 28, 37, 38 and 55-59 rejected under 35 U.S.C. 102(b) as being anticipated by Nuss et al., WO 02/20495.

Nuss et al., teaches several substituted anilinopyrimidines useful for treating diabetes and Alzheimer's disease, which include compounds, composition and method of use claimed in the instant claims. See page 6, formula 1 , page 7 formula IV and note with the given variable choices the compounds taught by Nuss et al., include instant compounds, composition and method of use. See example 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7-29, 31, 32, 34, 35, 37, 38 and 55-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuss et al., WO 02/20495.

Nuss et al., teaches several substituted anilinopyrimidines useful for treating diabetes and Alzheimer's disease, which include compounds, composition and method of use claimed in the instant claims. See page 6, formula 1 , page 7 formula IV and note with the given variable choices the compounds taught by Nuss et al., include instant compounds, composition and method of use. See example 16.

Nuss et al., differs in not exemplifying all compounds generically embraced in formula I or formula IV. But Nuss et al., teaches equivalency of various compounds exemplified including those in example 16 with those generically claimed.

Thus, it would have been obvious to one trained in the art at the time of the invention to select any of the species of the genus taught by the reference including those compounds claimed in the instant invention and expect the resultant compound to possess the use taught in the reference in view of equivalency teaching outlined above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-29, 31, 32, 34, 35, 37, 38 and 40-59, provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-24 of copending Application No. 10/702,113. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of instant claims namely compound, composition and method of use substantially overlap with claims 1-24 of the copending application. See formula I of instant claims and formula I of the copending application and note the overlap of various variable groups. Thus, it would have been obvious to one trained in the art at the time of the invention to select any of the species of the genus taught by the reference including those compounds claimed in the instant invention and expect the resultant compound to possess the use taught in the reference in view of equivalency of various compounds generically taught with those exemplified therein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 4-29, 31, 32, 34, 35, 37, 38 and 40-59, provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-60 of copending Application No. 10/638,784. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of instant claims namely compound, composition and method of use substantially overlap with claims 1-60 of the copending application. See formula I of instant claim 1 and formula I of the copending application and note the overlap of various variable

groups. Thus, it would have been obvious to one trained in the art at the time of the invention to select any of the species of the genus taught by the reference including those compounds claimed in the instant invention and expect the resultant compound to possess the use taught in the reference in view of equivalency of various compounds generically taught with those exemplified therein.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM.

The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

6/25/2006